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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,822	04/01/2002	Shigeo Ohta	2002_0256A	6325
513 7590 01/31/2006 WENDEROTH, LIND & PONACK, L.L.P. 2033 K STREET N. W. SUITE 800 WASHINGTON, DC 20006-1021			EXAMINER YAEN, CHRISTOPHER H	
			ART UNIT 1643	PAPER NUMBER

DATE MAILED: 01/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/049,822	Applicant(s) OHTA ET AL.	
	Examiner Christopher H. Yaen	Art Unit 1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 October 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution¹ as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-25 is/are pending in the application.
- 4a) Of the above claim(s) 6-8, 18-20 and 25 is/are withdrawn from consideration.
- 5) ☐ Claim(s) 13-16, 21 and 22 is/are allowed.
- 6) ☒ Claim(s) 1-5, 9-12, 17, 23 and 24 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>2/19/2002</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

RE: Ohta et al

Election/Restrictions

1. Applicant's election of group I in the reply filed on 10/07/2005 is acknowledged. Because applicant did not distinctly and specifically indicate whether the election of group I was with traverse, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 1-25 are pending, claims 6-8, 18-20, and 25 are withdrawn from further consideration as being drawn to a non-elected invention.

3. Claims 1-5, 9-17, and 21-24 are examined on the merits.

Priority

4. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Information Disclosure Statement

5. The Information Disclosure Statement filed 2/19/2002 is acknowledged and considered. A signed copy of the IDS is attached hereto.

Claim Rejections - 35 USC § 112, 2nd paragraph

6. Claims 1-5 and 9-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, base claim 1 and its dependents

Art Unit: 1643

are drawn to a genetically engineered cDNA molecule, wherein there are substitutions that change particular amino acids. The metes and bounds of the claim cannot be adequately determined because the preamble of the claim is drawn to nucleic acid, while the substitutions refer to amino acids.

Claim Rejections - 35 USC § 112, 1st paragraph

7. Claims 5, 11-12, 17, and 23-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a cell into which carries a recombinantly engineered cDNA of the rat *bcl-x* gene (i.e. SEQ ID No: 1), wherein the gene encodes a modified *bcl-x* protein having at least one substitution at amino acid positions 22, 26, 165, and

Art Unit: 1643

further comprising a protein-transduction domain. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

Applicants broadly claim a cell containing a recombinant vector containing a modified *bcl-x* gene. These claims encompass transgenic animals.

Quantity of experimentation

The quantity of experimentation in the areas of transgeneic animals, is extremely large given the unpredictability associated with transgeneic animals.

The unpredictability of the art and the state of the prior art

The specification teaches that there is no limitation on the types of cells used and encompasses a broad array of cell types ranging from prokaryotic cells to mammalian cells (see bridging page 8-9). Therefore, the claim reads on a cell within a transgenic animal given that the term "isolated" is not denoted in describing the cell. The breadth of the claim reads on the implementation of the transgenic cell in both *in vitro* and *in vivo* assays.

The state of the art at the time of filing was such that one of skill could not predict the phenotype of transgenics. For example, Overbeek (1994, "Factors affecting transgenic animal production," *Transgenic animal technology*, pages 96-98) taught that within one litter of transgenic mice, considerable variation in the level of transgene expression occurs between founder animals and causes different phenotypes (page 96,

Art Unit: 1643

last paragraph). The art of transgenic animals has for many years stated that the unpredictability lies, in part, with the site or sites of transgene integration into the target genome and that "the position effect" as well as unidentified control elements are recognized to cause aberrant expression of a transgene (Wall, 1996 Theriogenology, Vol. 45, pp. 57-68). The elements of the particular construct used to make transgenic animals are also held to be critical, and they must be designed case by case without general rules to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc. (Houdebine, 1994, J. Biotech. Vol. 34, pages 269-287, specifically page 281). Furthermore, transgenic animals are regarded to have within their cells, cellular mechanisms that prevent expression of the transgene, such as methylation or deletion from the genome (Kappell, 1992, Current Opinions in Biotechnology, Vol. 3, pp. 548-553).

Well-regulated transgene expression is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues (Cameron, 1997, Molec. Biol. 7, pages 253-265, specifically page 256, col. 1 -2, bridge paragraph). Factors influencing low expression, or the lack thereof, are not affected by copy number and such effects are seen in lines of transgenic mice made with the same construct (Cameron, 1997, Molec. Biol. 7, page 256, lines 3-9). With regard to the importance of promoter selection, Niemann (1997) states that transgenic pigs made with different promoters regulating expression of a growth hormone gene give disparate phenotypes - one deleterious to the pig, the other compatible with pig health (Niemann,

Art Unit: 1643

1997, Transg. Res. 7, pages 73-75, specifically page 73, col. 2, paragraph 2, line 12 to page 73, col. 1, line 4).

Examples in the literature aptly demonstrate that even closely related species carrying the same transgene construct can exhibit widely varying phenotypes. Mullins (1993, Hypertension, Vol. 22, pp. 630-633) states that not all animals express a transgene sufficiently to provide a model for a disease as the integration of a transgene into different species of animal has been reported to give divergent phenotypes. For example, several animal models of human diseases have relied on transgenic rats when the development of mouse models was not feasible. Mullins (1990, Nature, Vol. 344, 541-544) produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse *Ren-2* renin transgene. Hammer (1990, Cell, Vol. 63, 1099-1112) describes spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human β_2 -microglobulin transgenes. Both investigations were preceded by the failure to develop human disease-like symptoms in transgenic mice expressing the same transgenes that successfully caused the desired symptoms in transgenic rats (Mullins, 1989, EMBO J., vol. 8, pages 4065-4072; Taurog, 1988, Jour. Immunol., Vol. 141, pages 4020-4023). Mullins (1996, J. Clin. Invest. Vol. 98, pages S37-S40) disclose that the use of non-murine species for transgenesis will continue to reflect the suitability of a particular species for the specific questions being addressed, bearing in mind that a given construct may react very differently from one species to another. Thus, at the time of

Art Unit: 1643

filing, the phenotype of a transgenic cell contained within any animal was unpredictable and could not be prepared for any species.

Working examples

The specification provides no working examples for making the cells as broadly claimed. The specification provides little guidance to one of skill in the art in terms of how to make or use the instantly claimed invention. Therefore, coupled with the unpredictability of making transgeneic animals, as underscored by the prior art, the criticality of providing workable examples in an unpredictable art, such as transgeneic animals, is required for the practice of the instant invention.

Guidance in the specification

The specification provides limited guidance for the production and use of transgenic cells. What the specification does however provide, is the production of isolated cells comprising the said genetically engineered nucleic acid (see Example 2 for example).

Level of skill in the art

The level of skill in the art is deemed to be high.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the issue of the efficacy of the control and the negative teachings in the prior art balanced only against the high skill level in the

Art Unit: 1643

art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

It should be noted that if applicant amends the claims to reflect "isolated" cells, the instant rejection may be withdrawn.

Conclusion


Claims 13-16, and 21-22 appear to be free of the prior art. Claims 1-5, 9-12, 17, and 23-24 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H. Yaen whose telephone number is 571-272-0838. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Christopher Yaen
Art Unit 1643
December 22, 2005


CHRISTOPHER YAEN
PATENT EXAMINER